REMARKS

Examination of claims 1-16 is reported in the present Office Action. Claim 16 was objected to under 37 C.F.R. § 1.75(c) and the specification was objected to as including certain informalities. Claims 7, 9, 11, 13, and 15 were rejected under 35 U.S.C. § 112, first paragraph, claims 7-15 were rejected under 35 U.S.C. § 112, second paragraph, and claims 1-15 were rejected under 35 U.S.C. § 102. Each of the objections and rejections is addressed as follows.

Claim Objection

Claim 16 was objected to under 37 C.F.R. § 1.75(c) as being in improper multiple dependent form. As is noted above, claim 16 has been amended to depend from only one claim, and thus is no longer in multiple dependent form.

Objections to the Specification

The specification was objected to for not including a sequence identification number for the sequence at page 7, line 5. This objection has been met by the present amendment to page 7, which adds a reference to SEQ ID NO:1 after the sequence on this page. In the interest of completion, and as is noted above, applicants also have added a sequence identification number (SEQ ID NO:2) after the sequence appearing on page 31 of the specification. No new matter has been added by these amendments.

The Office Action also has required the insertion of a reference to the brief description of the drawings on page 20, line 21. Such a reference has been added by the present amendment, as is indicated above.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 7, 9, 11, 13, and 15 were rejected under 35 U.S.C. § 112, first paragraph, with the Office Action stating that "the specification, while being enabling for the disclosed proteins of Helicobacter pylori and immunogenic fragments therefrom, does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Original claim 7, from which the other rejected claims depend, originally specified that the protein or polypeptide of this claim can include a mutation, and this rejection appears to be based upon the assertion that no particular positions where such mutations could be tolerated have been described. This rejection has been met by the present amendment to claim 7, which eliminates references to proteins or polypeptides that include mutations.

For the record, applicants note that claim 7 retains its original reference to protein fragments, and has been amended to specify that these fragments are immunogenic. As is noted above, the Office Action has stated that such immunogenic fragments are enabled. In addition, support for the term "immunogenic fragment" can be found throughout the specification. For example, at page 8, lines 20-23 a "polypeptide" is defined as designating a product derived from a protein by fragmentation or mutation, and on page 11, line 38 through page 12, line 10, it is stated that the invention includes "a method for inducing an immune response against Helicobacter... in a mammal, according to which an immunologically effective quantity of a protein or of a polypeptide according to the invention is administered to the said mammal so as to develop an immune response..." The polypeptide of this method, in being used to induce an immune response, is inherently immunogenic, and, according to the definition of "polypeptide" noted above, includes a product derived by fragmentation. Thus, the term "immunogenic

fragment," as now is specified in claim 7, is supported by the present specification and, as noted by the Examiner, is enabled.

As is noted above, the other claims rejected under § 112, first paragraph, claims 9, 11, 13, and 15, depend from claim 7, and this was the basis for the rejection of these claims under § 112, first paragraph. Thus, the amendment of claim 7 to overcome this rejection is effective with respect to these claims as well.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 7-11 and 12-15 were rejected under § 112, second paragraph on several grounds, which are addressed as follows.

Claim 7 was rejected for including the phrase "by fragmentation and/or mutation" on the basis that the size, nature, and means of the fragmentation are not clear because, according to the Office Action, the claim could encompass a single amino acid. This rejection has been overcome by amendment of claim 7 to specify immunogenic fragments, as suggested in the Office Action. Support for this amendment is found throughout the specification, as is discussed above in reference to the rejection under § 112, first paragraph.

Claim 7 was also rejected under § 112, second paragraph for including the term "capable of." This rejection has been overcome by the present amendment to this claim, in which this term has been deleted from the claim. Claim 7 was further rejected for including the term "and/or," which, as is noted above, has been deleted from the claim as well.

Claims 8-11 were rejected because of a lack of antecedent basis for the terms "a protein or a polypeptide" in the claims from which they depend. As is noted above, these claims have been amended to include proper antecedent basis for all terms.

Claims 12 and 13 were rejected for not further limiting the claims from which they depend. These claims have now been canceled, without prejudice.

Claims 14 and 15 were rejected for reciting method steps in the passive voice. This rejection has been overcome by the present amendment to claims 14 and 15, in which these claims have been amended to recite steps in a positive manner, as was suggested in the Office Action.

Rejections under 35 U.S.C. § 102

Claims 1-15 were rejected under § 102 over several references, each of which is discussed below.

Several of the cited references[1] describe fractionation of Helicobacter protein preparations on gels, and detection of bands on these gels that have sizes that are similar to the sizes of the proteins now claimed. Some of these references, as well as two additional references,[2] also describe antibodies that recognize proteins having these or similar sizes. None of the cited references anticipate the compositions now claimed. In particular, as is noted above, the claims are now drawn to compositions that consist essentially of particular proteins in a pharmaceutically acceptable form or antibodies that recognize these proteins. The Helicobacter protein preparations of the cited references each include numerous proteins and, thus, even if

[1] Landini et al., Microbiologica 12:181-188, 1989
Husson et al., Infection and Immunity 61:2694-2697, 1993
Calenoff, U.S. Patent No. 5,567,594
Bölin et al., Journal of Clinical Microbiology 33:381-384, 1995
Doig et al., Infection and Immunity 62:4526-4533, 1994
Alemohammad, U.S. Patent No. 5,262,156
Pronovost et al., U.S. Patent No. 5,846,751
Pronovost et al., U.S. Patent No. 5,814,455

[2] Cordle et al., U.S. Patent No. 5,260,057
Ruiz et al., WO 94/06474

they were found to include the proteins of the present claims, they do not "consist essentially of" these proteins. In addition, even if these proteins were found to be present in the gels on which the protein preparations of the cited references were fractionated, their presence in such gels cannot be considered to be in a "pharmaceutically acceptable form," as is required by the present claims. In addition, the antibodies described in the cited references are present in mixtures of antibodies, and thus are not present in compositions that "consist essentially of" these antibodies, as is required by the present claims. Thus, the rejections of the present claims over the references listed in the footnotes should be withdrawn. Each of the additional rejections under § 102 is now addressed.

Claims 1, 2, 7-9, and 15 were rejected under § 102(b) as being anticipated by Ferrero et al. (Proc. Natl. Acad. Sci. U.S.A. 92:6499-6503, 1995), which describes a Helicobacter protein, designated HspB, which has a molecular weight of about 54 kDa. Similarly, claims 1, 2, 10, and 14 were rejected under § 102(b) as being anticipated by Leying et al. (Molecular Microbiology 6:2863-2874, 1992), which describes the Helicobacter flagellin A protein, which has a molecular weight of about 53.2 kDa. These rejections may now be withdrawn, because, as is noted above, claim 2 has been canceled and none of the other claims specify a 54 kDa Helicobacter protein unless in a context that is not mentioned in the cited references (see claims 29-32, above).

For the record, applicants note that deletion of reference to the 54 kDa protein from the rejected claims is not an admission that this protein is indeed identical to those described in the cited references. The amendment was made in the interest of expediting prosecution, and applicants reserve the right to pursue claims to the 54 kDa protein and compositions containing this protein in future applications.

CONCLUSION

Enclosed is a Petition to extend the period for replying to the Office Action for two months, to and including October 31, 2001, as well as a check in payment of the required fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095. In addition, in the event that any further issues remain in this case, applicants respectfully request that the Examiner contact the undersigned by telephone prior to taking any further actions on the merits.

Respectfully submitted,

Date: October 31, 2001

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The paragraph on page 7, lines 3-19 was amended to add a sequence identification number after the amino acid sequence in this paragraph, as follows:

The N-terminal sequence of the 50 kDa protein of an *H. pylori* strain (ATCC 43579) is as follows (one-letter code): MKEKFNRTKPHVNIGTIGHVDH (SEQ ID NO:1). This information does not exclude the fact that equivalent proteins capable of being purified according to the process indicated above can have a slightly different N-terminal sequence, since they may be derived from another bacterial strain. Such a difference would indeed reflect the phenomenon of allelic variance commonly encountered within the same species. For example, a bacterial species is usually represented by a group of strains which differ from each other in minor allelic characteristics. A polypeptide which fulfils the same biological function in different strains may have an amino acid sequence which is not different for all the strains. Such an allelic variation also exists in DNA.

The paragraph on page 31, lines 3-5 was amended to add a sequence identification number after the amino acid sequence in this paragraph, as follows:

(iii) A monomeric form at 54 kDa in SDS-PAGE with the following N-terminal sequence: MVNKDVKQTTAFGAPVWDDNNVITAGPRG (SEQ ID NO: 2).

Line 20 on page 37 was amended to correct a sequence identification number, as follows:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: [1]2:

1. (Amended) A composition consisting essentially of a *Helicobacter pylori* [protein in a substantially purified form, capable of being obtained from an *H. pylori*] membrane fraction protein in a pharmaceutically acceptable form, wherein said protein has a [, and whose] molecular weight that [after electrophoresis on a 10% polyacrylamide gel in the presence of

SDS] appears to be of the order of [54,] 50, 32-35, or 30 kDa[;] after electrophoresis on a 10% polyacrylamide gel in the presence of SDS [provided that when the molecular weight is 54 kDa, the protein does not react with an anti-catalase antiserum].

3. (Amended) The composition of [Protein according to] claim 1, wherein the [whose] apparent molecular weight of the protein is of the order of 50 kDa and the protein is obtainable [which is capable of being obtained] by a process in which:

(i) [the] *H. pylori* bacteria are extracted with 1% n-octyl β-D glucopyranoside, followed by centrifugation;

(ii) a bacterial pellet is recovered and it is treated with lysozyme and subjected to sonication, followed by centrifugation;

(iii) a centrifugation pellet is recovered and it is subjected to washing with 20 mM Tris-HCl buffer pH 7.5, followed by centrifugation;

(iv) the membrane fraction consisting of the centrifugation pellet is recovered and it is resuspended in aqueous medium;

(v) the membrane fraction is subjected to an anion-exchange chromatography on a Q-Sepharose column in a 0-0.5 M NaCl gradient, followed by washing in 1 M NaCl;

(vi) the fraction eluted at the start of washing in 1 M NaCl is recovered and it is subjected to an anion-exchange chromatography on a DEAE-Sepharose column, in a 0-0.5 M NaCl gradient; and

(vii) the fraction eluted in 0.3-0.4 M NaCl is recovered.

4. (Amended) The composition of [Protein according to] claim 3, wherein the protein [which] has as N-terminal sequence the amino acid sequence as shown in SEQ ID NO:1.

5. (Amended) The composition of [Protein according to] claim 1, wherein the [whose] apparent molecular weight of the protein is of the order of 30 kDa and the protein is obtainable [which is capable of being obtained] by a process in which:

(i) [the] *H. pylori* bacteria are extracted with 1% n-octyl β-D glucopyranoside, followed by centrifugation;

(ii) a bacterial pellet is recovered and it is treated with lysozyme and subjected to sonication, followed by centrifugation;

(iii) a centrifugation pellet is recovered and it is subjected to washing with 20 mM Tris-HCl buffer pH 7.5, followed by centrifugation;

(iv) the membrane fraction consisting of the centrifugation pellet is recovered and it is resuspended in aqueous medium;

(v) the membrane fraction is subjected to an anion-exchange chromatography on a Q-Sepharose column in a 0-0.5 M NaCl gradient;

vi) the fraction eluted in 0.28-0.35 M NaCl is recovered and it is subjected to an anion-exchange chromatography on a DEAE-Sepharose column, in a 0-0.5 M NaCl gradient; and

(vii) the fraction corresponding to the direct eluate is recovered (absence of NaCl).

6. (Amended) The composition of [Protein according to] claim 1, wherein the [whose] apparent molecular weight of the protein is of the order of 32-35 kDa and the protein is obtainable [which is capable of being obtained] by a process in which:

(i) [the] *H. pylori* bacteria are extracted with 1% n-octyl β-D glucopyranoside, followed by centrifugation;

(ii) a bacterial pellet is recovered and it is treated with lysozyme and subjected to sonication, followed by centrifugation;

(iii) a centrifugation pellet is recovered and it is subjected to washing with 20 mM Tris-HCl buffer pH 7.5, followed by centrifugation;

(iv) the membrane fraction consisting of the centrifugation pellet is recovered and it is resuspended in aqueous medium, advantageously in carbonate buffer pH 9.5;

(v) the suspension obtained in (iv) is centrifuged at about 200,000 x g and the supernatant is recovered;

(vi) the pH of the supernatant obtained in (v) is reduced to about pH 7, advantageously by dialysing against phosphate buffer pH 7;

(vii) the preparation obtained in (vi) is subjected to a cation-exchange chromatography on an SP-Sepharose column in a 0 - 0.5 M NaCl gradient, advantageously in a phosphate buffer pH 7; and

(vii) the fraction eluted in 0.26 - 0.31 M NaCl is recovered.

7. (Amended) A Helicobacter protein, or a polypeptide that is derived from the protein by fragmentation, [and/or mutation,] in a substantially purified form, which is [capable of being]

recognized by an antiserum raised against the [a] protein of the composition of [according to] claim 1.

10. (Amended) A composition consisting essentially of a monospecific [Monospecific] antibody that recognizes [capable of recognizing a] the protein [or a polypeptide according to] of the composition of claim 1.

11. (Amended) A composition consisting essentially of a monospecific [Monospecific] antibody that recognizes [capable of recognizing a] the protein or polypeptide [according to] of claim 7.

14. (Amended) A diagnostic [Diagnostic] method for detecting [which makes it possible to detect] the presence of Helicobacter in a biological sample, according to which the biological sample is brought into contact with the [an] antibody of [according to] claim 10 so that an immune complex forms, the unbound material is [optionally] removed, and the immune complex formed between the sample and the antibody is detected.

15. (Amended) A diagnostic [Diagnostic] method for detecting [which makes it possible to detect] the presence of antibodies to Helicobacter in a biological sample, according to which the biological sample is brought into contact with the protein or [a] polypeptide of claim 1 or claim 7 so that an immune complex forms, the unbound material is [optionally] removed, and the immune complex formed between the sample and the protein or polypeptide is detected.

16. (Amended) A process [Process] for the purification of [a] the protein [or of a polypeptide according to] of the composition of claim 1 from a biological sample, according to which the biological sample is subjected to [an] affinity chromatography using a monospecific antibody that recognizes said protein or polypeptide [according to Claim 10].